

From the Medical Department of the University Canton Hospital in Zürich

Director: Prof. Dr. Wilhelm Löffler

Work performed under the Direction of P.-D. Dr. med. Fritz Koller

The Influence of Internal Disease, Particularly Liver Disease on the Total Excretion of 17-Ketosteroids

INAUGURALDISSERTATION

for the Degree of Doctor of Medicine
from the Medical Faculty of the University of Zürich

Presented by

Alvin Goldman

of New York City, U.S.A.

Accepted on the Proposal of Prof. Dr. W. Löffler and P.-D. Dr. F. Koller

Zürich 1953

Buchdruckerei Fluntern

Plattenstrasse 27

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*Dedicated
to my dear mother
and
to the memory of my dear father*

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I. INTRODUCTION

The 17-ketosteroids are a group of chemical compounds possessing a ketone group at the C 17 position of the steroid ring system. They are secreted by the adrenal cortices and the interstitial cells of the testes as steroids and are excreted in part as the final breakdown product in the urine. The human ovary is, however, only an insignificant source of neutral 17-ketosteroids. Accordingly, the measurement of the 17-ketosteroids provides a biochemical index of testicular and adrenocortical activity.

The 17-K. S. that have been isolated are divided into groups, namely the alpha and beta K. S. The alpha group arises from the adrenal cortical and gonadal secretions while the beta group originate exclusively from the adrenal cortex. The total amount of beta 17-K. S. excreted is essentially the same in both sexes and they are often used to determine quantitatively the relative proportion to the total output. (1). The two groups differ from each other chemically in the spatial or steric position of the OH group at the number 3 atom.

The normal daily excretion values that have been determined by several different workers vary only slightly. They are described in terms of mg./24 hrs. Talbot, Butler, and MacLachlan reported the following average results in a normal series study (2):

Children under the age of 7	— 1.3 mg.
Children aged 7—12	— 4.0 mg.
Children aged 12—15	— 8.2 mg.
Adults, male	— 15.0 mg.
Adults, female	— 10.2 mg.
Pregnant women	— 15.1 mg.

Patterson, McPhee, and Greenwood in their series of normal cases, found male excretions ranging from 9.4 to 20.9 mg. with a mean of 13.3 and female excretions ranging from 3.5 to 14.6 mg. with a mean of 7.4 (3).

They were also of the opinion that there is a direct relation between body size and 17-K. S. excretion. Forbes, Donaldson, Reifenstein and Albright, in a series of 73 normal male and 65 female subjects, found daily excretions ranging from 6.7 to 27.2 mg. in the males and 3.8 to 16.9 mg. in the females (4). Furthermore, these authors generally agree that a) the excretion of the 17-K. S. is very low at birth, b) the value gradually increases with age reaching a maximum between the second and fourth decades of life and is followed by a gradual decrease, although never reaching lower than approximately one third of the maximum, and

c) the amount excreted during sleep is less than the amount excreted during waking hours.

The principal members of the 17-K.S. group which have been isolated from the urines of normal individuals are androsterone, etiocholanolone, isoandrosterone, and dehydroisoandrosterone. The first two of these arise in part from the testes while all represent the excretion products of some of the steroids of the adrenal cortex. Some of the other neutral 17-K.S. are androstandiol-3(α)-11(β)-on-17, discovered in the urine of a patient with a neoplasm of the adrenal cortex by Mason and his coworkers in 1945 (5), 11-hydroxy-etiocholanol-3(α)-on-17 discovered by Lieberman and his coworkers (6), and iso-androstenolone, isolated from the urine of a 2 year old girl with virilism who had an adrenal cortical tumor by Huis in't Veld, and Hartogh-Katz in 1948 (7). There have been several others isolated since.

The determination of the neutral 17-K.S. of urine was first developed by Zimmermann in 1935 (8). The determination is based on the principle

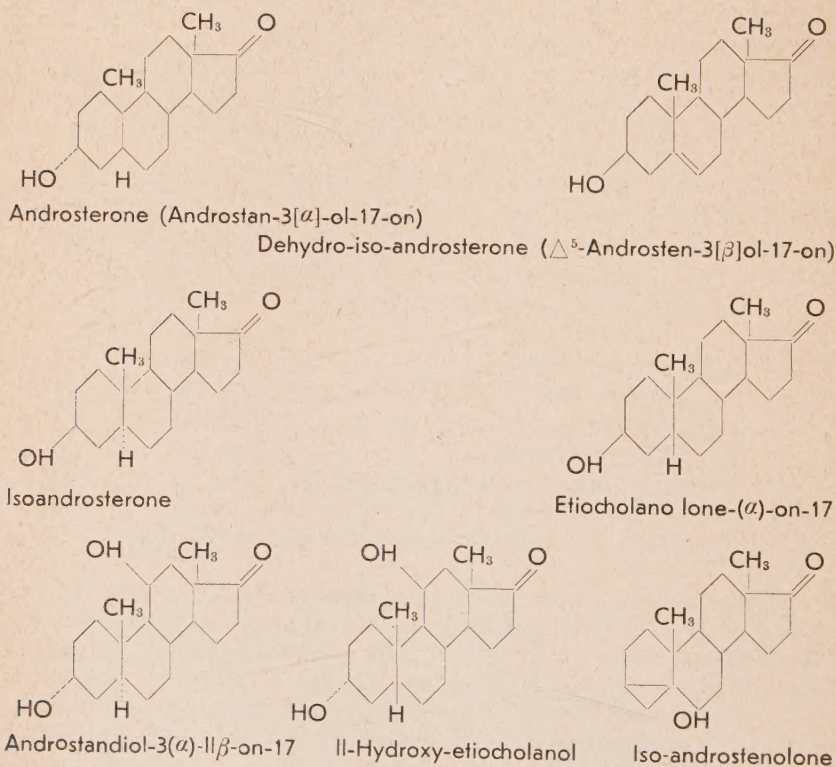


Fig. 1: The Chemical Formulas of Some of the Neutral 17-K.S.

of first setting free the steroids of the urine from their water-soluble conjugates by acid hydrolysis and then extracting with ether or benzene. After removal of the impurities with extraction, the 17-K.S. content of the neutral residue is ascertained by quantitative application of the Zimmermann reaction. This comprises coupling of the reactive 17-ketone groups of the compounds, in an alkaline state, with m-dinitrobenzene to form colored complexes, the intensity of which in the green region of the spectrum is measured in the photoelectric colorimeter and compared with the color developed by the known quantities of the pure crystalline 17-K. S.

More recently, quantitative chromatographic separation has been utilized for the determination of the 17-K.S. The method used for the determinations in this survey is that of Dingemans and Huis in't Veld (9). The 17-K. S. are separated quantitatively into specific groups. Subsequent to hydrolysis and extraction, the 17-K.S. are absorbed by Al oxide and react with variable intensity with this absorbant depending on their individual structure. By elution with an organic solvent and the gradual addition of alcohol, the less absorbed of the ketosteroids appear or disappear in their tubes with greater speed. A total of 8 groups have been separated in this way. Several other similar methods have been devised and are used in various other laboratories.

II. SURVEY and RESULTS

In an effort to further determine the effect of internal diseases on 17-K.S. excretion, a study was made of 138 medical patients who were hospitalized at the University cantonal hospital in Zürich and whose 24 hour urine specimens were measured for their total 17-K.S. content. Determinations were made on the urines of groups of patients suffering, or suspected of suffering from endocrine disorders, on the urines of patients with parenchymal liver disease and metabolic disorders, and on the urines of patients with acute or chronic illnesses. In addition, this test was performed on the urines of a group of patients who received ACTH or cortisone to measure the effect of this therapy on adrenal cortical activity.

In this study emphasis was placed on the influence of liver disease on 17-K.S. excretion and the possible application of the 17-K.S. determination in following the progress of the disease.

The cases were classified in groups according to the type of the disease and these were tabulated with the respective diagnoses and excretion values. These groups include endocrine disorders, liver disease, metabolic disorders, and acute and chronic illnesses. In addition a comparison was made of the results of the liver function tests with 17-K. S. excretion in patients with liver diseases.

Excretion of 17-K.S. in Patients with Endocrine Disorders

There were 7 cases of Addison's disease in the study. As is seen in Table 1, each of the patients had markedly reduced 17-K. S. output with an average of 3 mg./24 hours. One female patient with an excretion of 0.6 mg. expired shortly after the determination.

The remaining patients with endocrine disorders include the following: 4-castration or bilateral orchidectomy, 1-bilateral testicular atrophy, 3-Morbus Cushing, 4-hypopituitarism, 2-cranial tumors, 1-acromegaly, 1-diabetes insipidus, 1-hyperthyreosis, 1-mixedema, 1-post strumectomy, 3-strumas, 1-carcinoma of the pancreas, 1-post operative parathyroid tetany, 1-amenorrhea of psychogenic origin, and 1-unilateral adrenalectomy following hyperplasia. 17-K. S. output in these patients was as follows, Table 2:

Extremely low output was measured in all cases of hypopituitarism, cranial tumors, diabetes insipidus, hyperthyreosis, and 3 of the 4 cases of castration and orchidectomy.

Moderately reduced excretion was measured in one of the cases of Morbus Cushing, the post strumectomy, mixedema, acromegaly, and one each of the cases of struma nodosa and post castration.

Normal values were observed in one of the cases of Morbus Cushing, the cases of testicular atrophy, carcinoma of the pancreas, postoperative parathyroid tetany, the psychogenic amenorrhea, and 2 cases of struma nodosa.

An abnormally high output was measured in the urine of the patient with the unilateral adrenalectomy and a slight increase in output was observed in one case of Morbus Cushing.

Table 1
17-K. S. Excretion of Patients with Addison's Disease

Pat.	Sex	Age	17-K.S. mg. 24 hrs.
1. R. F.	M	44	3.6
2. S. E.	M	51	6.3
3. M. L.	M	44	2.4
4. B. E.	F	61	1.7
5. B. M.	F	19	2.0
6. G. A.	F	48	0.6
7. W. M.	F	48	3.6

mg/24 hrs.

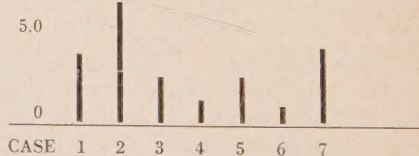
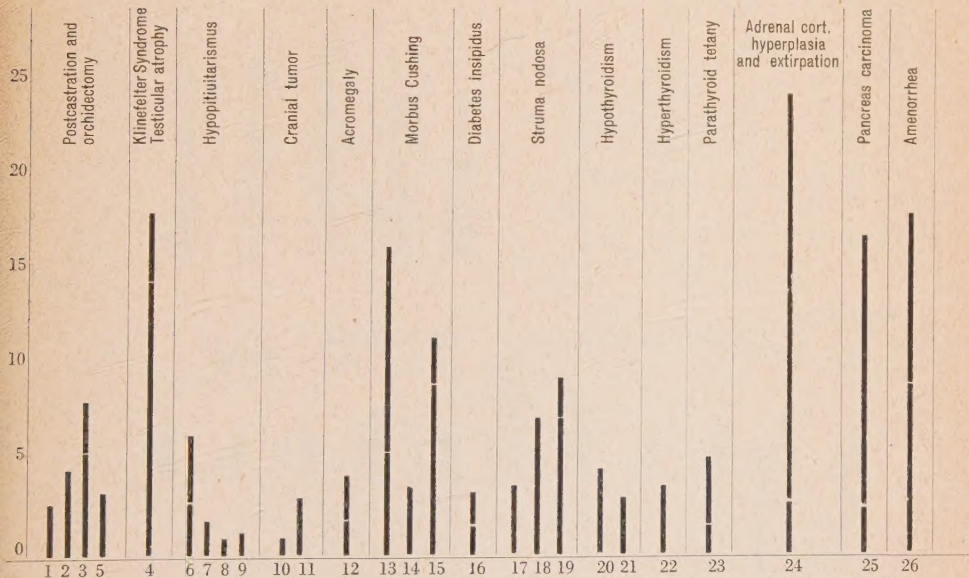


Table 2

17-K. S. Excretion of Patients with Endocrine Disorders

Pat.	Sex	Age	17-K.S. mg. 24 hrs.	Pat.	Sex	Age	17-K.S. mg. 24 hrs.
1. G. A.	M	52	2.9	14. A. M.	F	53	3.8
2. K. K.	M	33	4.8	15. S. R.	M	43	11.4
3. B. H.	M	75	8.1	16. M. R.	M	26	3.4
4. S. R.	M	25	18.0	17. V. F.	F	48	3.5
5. M. F.	M	64	3.2	18. V. E.	F	40	7.5
6. S. R.	M	49	6.4	19. S. S.	F	35	9.3
7. A. M.	F	47	1.5	20. K. O.	F	45	4.5
8. S. E.	F	39	0.8	21. H. I.	F	44	3.1
9. S. R.	F	55	0.9	22. W. E.	M	46	3.4
10. M. J.	M	48	0.3	23. B. R.	F	34	5.0
11. S. E.	F	47	3.3	24. T. S.	F	26	24.4
12. S. A.	F	40	4.1	25. E. H.	M	49	16.4
13. G. K.	F	44	16.1	26. C. M.	F	22	8.1

mg/24 hrs

*Excretion of 17-K.S. in Patients with Liver Disease*

There were a total of 25 cases of liver disease observed. As seen in Table 3, 15 of these were patients suffering from Laennec cirrhosis, (14 had histories of chronic alcoholism and one had a recent history of brucellosis).

The other cases included 5 patients with infections hepatitis, and one each respectively with pseudo hepatic cirrhosis Friedl-Pick, hema-

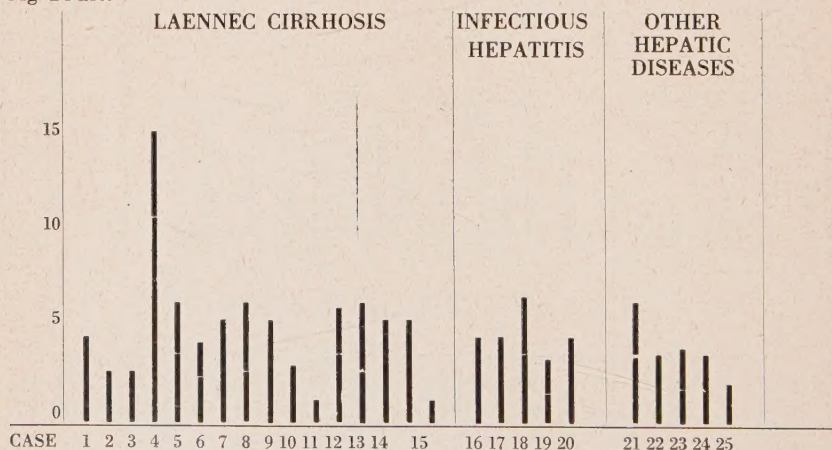
chromatosis, biliary cirrhosis, cholelithiasis with some obstruction, and a patient with a long history of amebic dysentery.

With the exception of one case of Laennec cirrhosis, explained on the basis of an earlier brucellosis, all the patients excreted 17-K.S. in significantly reduced quantities. The average was 3.2 mg. in males and 3.6 mg. in females. One female patient with Laennec cirrhosis had an output in the lower normal range, 5.5 mg., on her first admission but which was markedly reduced to 1.1 mg. when measured later again on her second admission 4 months later.

Table 3
17-K.S. Excretion of Patients with Liver Diseases

Pat.	Sex	Age	17-K.S. mg. 24 hrs.	Pat.	Sex	Age	17-K.S. mg. 24 hrs.
1. C. F.	M	45	4.9	14. R. P.	M	44	5.1
2. D. A.	M	55	2.5	15. S. M.	F	48	5.5
3. F. G.	M	60	2.5				1.1
4. G. E.	M	52	14.9	16. B. O.	M	44	4.7
5. M. S.	M	58	6.4	17. A. K.	F	32	4.7
6. P. A.	M	53	4.0	18. S. U.	M	27	6.7
7. P. R.	M	53	5.3	19. P. M.	F	22	3.2
8. R. M.	M	61	6.4	20. S. D.	F	50	4.5
9. S. J.	M	64	5.1	21. S. W.	M	41	6.1
10. W. E.	M	55	2.7	22. L. A.	M	39	3.6
11. W. R.	M	57	1.0	23. R. I.	F	44	4.0
12. Z. E.	M	36	5.6	24. D. F.	F	40	3.6
13. L. J.	M	62	6.4	25. W. J.	F	46	2.3

Mg/24 hrs.



Excretion of 17-K.S. in Patients with Liver Disease After Administration of Testosterone

The influence of testosterone on 17-K.S. excretion in patients with liver disease was determined by the following method: 11 patients with liver cirrhosis, 7 patients with epidemic hepatitis, and 5 healthy persons received 50 mg. of testosterone propionate i.v. Urinary 17-K.S. determinations were made 1 day before and after the injections. Fig. 2 shows the differences in the total 17-K.S. urinary output before and after the administration of the testosterone, in the different persons tested. From the results it can be seen that further evidence is available to show the significantly low 17-K.S. excretion values in patients with liver disease. Also significant is the apparent lower increase in output of the patients with liver disease as compared to the increase in output of the healthy individuals, subsequent to the testosterone administration.

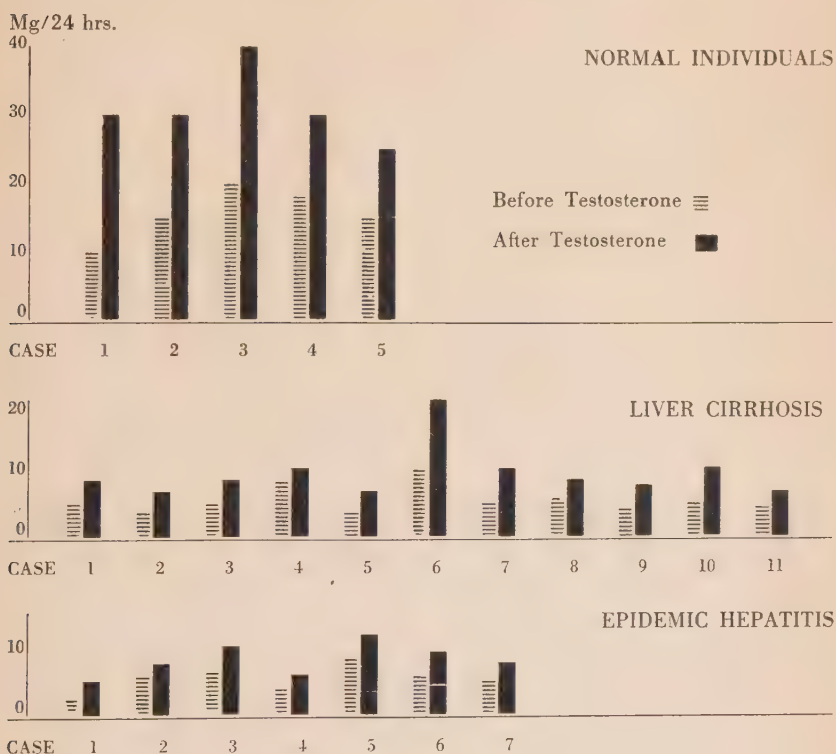


Fig. 2 - 24 hr. 17-K.S. excretion in the urine of healthy individuals and patients with liver cirrhosis and epidemic hepatitis before and after intravenous injection of 50 mg. of testosterone propionate.

TABLE 4

A Comparison of the Results of Liver Function Tests with 17-Ketosteroid Excretion

Pat.	Sex	Age	Liver	Skin and Hair type	Sed. Rate	Ceph. flocc.	
1.	C. F.	M	45	2 finger breaths below co- stal margin. Smooth, indolent.	Hair scanty	25/35	—
2.	D. A.	M	55	2, firm, indolent.	Hair scanty	41/53	—
3.	F. G.	M	60	4—5, firm, smooth, indol.	Venous stasis. Hair scanty.	48/52	++
4.	G. E.	M	52	2, firm, smooth, indol.	Hair scanty.	18/27	+++
5.	M. S.	M	58	3, indol., ascites.	Icteric, hair scanty	25/32	+++
6.	P. A.	M	53	1, firm, indolent.	Hair scanty	45/53	+++
7.	P. R.	M	53	2—3, dolent.	Hair scanty	17/27	++
8.	R. M.	M	61	3—4, firm, smooth, indolent.	Subicteric	31/49	—
9.	S. J.	M	64	2—3, firm, smooth, indolent.	Hair scanty	53/55	+
10.	W. E.	M	55	1—2, firm, smooth, indolent.	Hair scanty	50/55	+
11.	W. R.	M	57	1, smooth, indolent.	Caput medusae, hair scanty.	50/54	++
12.	Z. E.	M	36	3, firm, dolent.	Subict., hair scanty	33/49	—
13.	L. J.	M	62	2, firm, smooth, indol.	Spiders, hair scanty	28/34	—
14.	S. M.	F	48	Iliac crest, firm.	Axillary hair scanty.	58/61	+++
2nd Admission 4 months later-					69/76	+++	
15.	B. O.	M	44	2, smooth, dolent.	Icteric	20/29	+++
16.	A. K.	F	32	1—2, smooth, dolent.	Icteric	36/50	+++
17.	S. U.	M	27	2, smooth, indolent.	Icteric	31/47	+
18.	P. M.	F	22	2, smooth, dolent.	Subicteric	45/49	++++
19.	S. D.	F	50	2, firm, indolent.	Subicteric	24/36	++
20.	S. W.	M	41	3, firm, ascites	Hair scanty.	10/22	++
21.	L. A.	M	39	5, firm, smooth, indol.	Dark brown pigment.	37/48	++
22.	R. I.	F	44	2, firm, smooth, indol.	Subicteric	30/48	+
23.	W. J.	F	46	1—2, normal consistency.	No changes.	14/24	—

in Patients with Liver Disease

Weltmann	Quick	Bromsulph. Retention		Serum bil.	Diagnosis	17-K.S. mg. 24 hrs.
1. 0. 35	100%			1.6	Laennec cirrhosis	4.9
2. 0. 35	90%	I 8%	II 0%	0.6	Laennec cirrhosis	2.5
3. 0. 30	80%	I 29%	II 25%	5.4	Laennec cirrhosis	2.5
4. 0. 25	60%	I 29%	II 10%	2.5	Laennec cirrhosis post Bang.	14.9
5. 0. 35	60%			17.3	Laennec cirrhosis, hepatoma.	6.4
6. 0. 18	80%	I 36%	II 12%	1.1	Laennec cirrhosis	4.0
7. 0. 15	30%	I 69%	II 53%	2.3	Laennec cirrhosis	5.3
8. 0. 25	70%	I 18%	II 16%	7.4	Laennec cirrhosis	6.4
9. 0. 45	90%			2.1	Laennec cirrhosis	5.1
10. 0. 40	90%	I 17%	II 13%	2.0	Laennec cirrhosis	2.7
11. 0. 15	70%	I 22%	II 20%	2.4	Laennec cirrhosis	1.0
12. 0. 20	80%	I 29%	II 18%	3.6	Laennec cirrhosis	5.6
13. 0. 25	90%	I 17%	II 6%	1.3	Laennec cirrhosis	6.4
14. 0. 20	80%	I 17%	II 6%	2.9	Laennec cirrhosis with	5.5
0. 15	70%	I 18%	II 6%	4.8	esophageal varices.	1.1
15. 0. 18	80%	I 27%	II 15%	29.8	Infectious hepatitis	4.7
16. 0. 20	50%			15.3	Infectious hepatitis	4.7
17. 0. 15	80%			16.6	Infectious hepatitis	6.7
18. 0. 18	80%			11.5	Infectious hepatitis	3.2
19. 0. 18	80%			8.3	Infectious hepatitis	4.5
20. 0. 20	80%			2.1	Pseudo hepatic cirrhosis	
					Friedl-Pick.	6.1
21. 0. 25	90%	I 39%	II 20%	1.5	Hemachromatosis with cirrhosis	3.6
22. 0. 25	70%			4.9	Cholelethiasis with obstruction.	4.0
23. 0. 18	100%	I 13%	II 9%	0.5	Long history of amebic	
					dysentary.	2.3
Norm- 0.25- 0.30	Norm- 70%+	Norm- I 6% 15 min. II 0% 30 min.		Norm-1.3 mg.%		Norm F -5-15 mg. M 10-20 mg.

Comparison of the Liver Function Test Results with 17-K. S. Output

The results of the liver function tests were compared with the output of 17-K. S. in an effort to determine if any correlation exists between them. The liver function tests used for comparison included the cephalin flocculation, Weltmann reaction, Quick, Bromsulphthalein retention, as well as the serum bilirubin. In some cases one of the tests were not performed. Table 4 shows the clinical and laboratory findings of each case studied.

Physical changes were observed in every case. These varied from slight liver enlargement in the patient with the long history of amebic dysentery to a large, firm, indolent liver associated with ascites, spiders, and female hair type in another with severe Laennec cirrhosis. The results of the tests demonstrated some reduction in function in all cases. Certain variations were however, noted. In case No. 2 for example all the liver function tests were negative despite the fact there were clinical signs of Laennec cirrhosis. The 17-K. S. output was; however, markedly reduced, 2.5. mg. In case No. 4 the liver function tests demonstrated liver damage but the 17-K. S. output was normal, 14.9 mg. In one interesting case No. 14 the patient, a 48 yr. old female chronic alcoholic and cirrhotic, had on her first admission significant positive liver function test results with a normal 17-K. S. output, 5.5 mg. However, 4 months later on her second admission, her 17-K. S. output was reduced to 1.1 mg.

Excretion of 17-K. S. in Patients with Metabolic and Deficiency Disorders

There were 19 cases in this group (Table 5). They included 9 patients with diabetes mellitus, 4 with sprue, 1 with pernicious anemia, 2 with dysproteinemia, 1 with gout arthritis, and 2 with obesity.

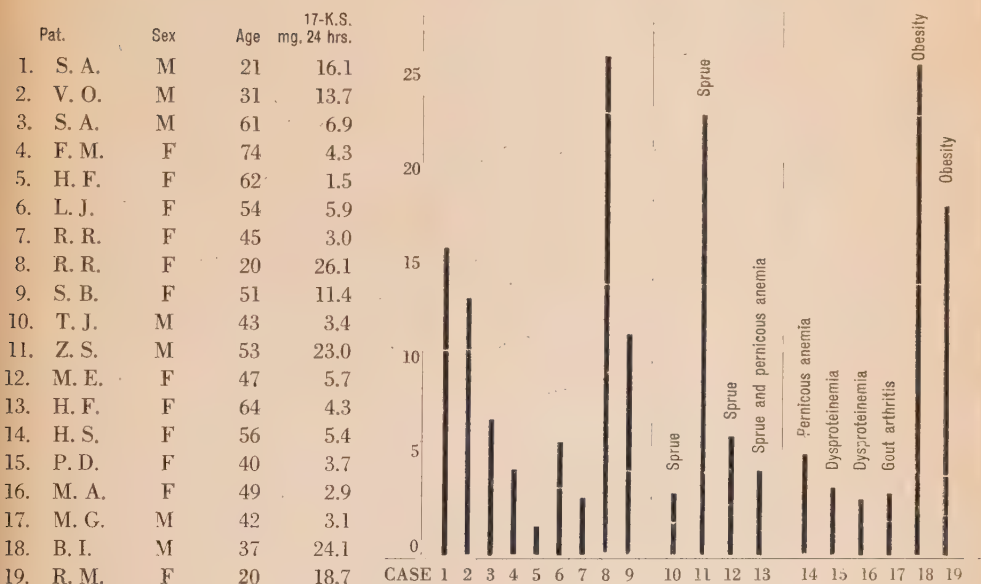
Of the diabetic patients, 4 had normal outputs, 4 had reduced values, 6.9 (M), 4.3, 1.5, 3.0 (F), and 1 20 yr. old girl who also suffered from obesity had an abnormally high output, 26.1 mg. Physical and laboratory examinations revealed in her case neither adrenal cortical nor pituitary hyperfunction.

In the cases of sprue 1 patient had a normal output, 2 had a reduced output, 3.4 (M), 4.3 (F), and 1 had an output slightly above normal, 23 mg. (M). The patient with pernicious anemia had a normal output. Both patients with dysproteinemias had reduced excretions, 3.7 and 2.9 mg. (F). The patient with gout arthritis had a markedly reduced output, 3.1 mg. (M). On the other hand both patients with obesity had above normal outputs, 24.1 mg. (M) and 18.7 mg. (F), respectively.

Table 5
17-K. S. Excretion of Patients with Metabolic and Deficiency Disorders

Mg./24 hrs.

Diabetes mellitus



*Excretion of 17-K. S. in Patients with Infectious, Inflammatory,
and Debilitating Diseases*

A total of 57 cases were observed in this group. They were subdivided into acute and chronic rheumatoid arthritis, cardiac and vascular diseases, malignant diseases, and chronic inflammatory and infectious diseases. Table 6 shows the individual patients with their respective 17-K. S. output.

Of the 11 patients suffering, from rheumatoid arthritis, 8 had below normal 17-K. S. excretion. The remaining 3 had excretion values in the lower norm.

Of the 19 patients suffering from cardiac vascular diseases, 13 had a reduced output. Many of these were markedly reduced, 0.9 (M), 2.8 (M), 1.8 (F), 2.3 (F), 1.5 (F) and 2.4 (F) mg. On the basis of the case histories, the lower values were found in those patients who were ill the longest.

There were 8 patients listed as suffering from malignant disease. Five of these had excretion values below normal. However, only one patient, a 16 yr. old girl suffering from Hodgkins's disease, had a markedly reduced output, 2.5 mg.

Listed also are 19 patients who suffered from chronic infectious and inflammatory diseases. 14 of these had excreted reduced quantities of 17-K. S. The lowest values were found in the cases of pulmonary tuberculosis, 2.1 (M), 6.8 (M), 1.5 (F), 2.3 (F) mg., colitis, 2.3 (F) mg., and chronic eczema, 2.9 (F) mg. Duration of the illness appeared to play a significant role in reducing the output.

Table 6

17-K.S. Excretion of Patients with Infectious, Inflammatory, and Debilitating Diseases

Pat.	Sex	Age	17-K.S. Excretion mg. in 24 hrs.	Pat.	Sex	Age	17-K.S. Excretion mg. in 24 hrs.
<i>Rheumatoid Arthritis, Acute</i>				<i>Malignant Disease</i>			
1. B. E.	M	19	8.9	31. B. J.	M	64	8.3
2. H. F.	M	39	8.9	32. B. J.	M	61	7.0
3. O. F.	M	49	6.3	33. B. A.	M	48	11.6
<i>Rheumatoid Arthritis, Chronic</i>				34. K. A.	M	45	10.7
4. B. O.	M	59	7.2	35. M. K.	M	57	13.2
5. B. R.	M	55	10.3	36. K. E.	F	64	4.8
6. H. A.	M	33	12.2	37. T. M.	F	49	4.7
7. O. V.	M	36	5.6	38. W. R.	F	16	2.5
8. P. M.	M	30	12.4	<i>Chronic Inflammatory and Infectious Disease</i>			
9. F. A.	M	69	8.4	39. B. R.	M	53	9.8
10. B. M.	F	54	4.6	40. C. A.	M	48	9.6
11. W. A.	F	54	4.9	41. G. S.	M	33	2.1
<i>Cardiovascular Disease</i>				42. M. L.	M	19	8.0
12. B. A.	M	47	14.7	43. R. L.	M	57	5.2
13. D. R.	M	75	9.5	44. S. H.	M	40	6.3
14. E. B.	M	62	5.6	45. M. C.	M	32	11.8
15. G. K.	M	68	6.9	46. S. J.	M	29	6.8
16. G. F.	M	67	8.2	47. W. E.	M	48	5.6
17. K. A.	M	50	2.8	48. A. P.	F	26	4.6
18. M. A.	M	34	3.4	49. M. M.	F	56	1.5
19. M. E.	M	36	3.6	50. N. H.	F	59	6.0
20. M. H.	M	44	0.9	51. P. M.	F	65	2.3
21. S. A.	M	57	5.0	52. R. C.	F	36	7.7
22. B. J.	F	46	11.5	53. R. E.	F	46	6.2
23. C. M.	F	75	1.8	54. S. L.	F	20	4.6
24. E. I.	F	51	12.2	55. W. M.	F	24	9.5
25. F. I.	F	67	3.6	56. W. B.	F	46	3.4
26. H. B.	F	69	2.3	57. D. C.	F	49	2.9
27. H. E.	F	74	6.5				
28. L. M.	F	66	1.5				
29. M. M.	F	47	5.1				
30. S. R.	F	31	2.4				

Effect of ACTH and Cortisone on 17-K. S. Excretion

There were a total of 19 patients who received ACTH or cortisone therapy. 17-K. S. determinations were made on their 24 hour urine specimens prior to and subsequent to the therapy. Of the total, 6 received cortisone and 13 ACTH. In addition, a determination of one patient's urine 17-K. S. content was made 2 weeks following the cessation of ACTH therapy, No. 16. One patient No. 6 was started on cortisone but it was shortly replaced with ACTH.

Table 7 demonstrates the results. In every case where ACTH was given a significant rise in 17-K. S. excretion appeared within a few days after the initiation of the therapy. With cortisone, however, the reverse effect took place. Following this therapy, the 17-K. S. output decreased significantly. In the case where a determination was performed 2 weeks subsequent to the cessation of ACTH therapy No. 16, it was found that the total 17-K. S. excretion was lower than that excreted prior to the inauguration of the therapy. In the case where the original cortisone therapy was replaced with ACTH, No. 6, the 17-K. S. content increased to a value higher than that measured prior to the original cortisone therapy.

Table 7
The Effect of Cortisone and ACTH on 17-K. S. Excretion

Pat.	Sex	Age	Diagnosis	Therapie	17-K. S. mg. 24 hrs.	
					Before	After
1. B. O.	M	59	Chronic rheum. arthritis	Cortisone	7.2	4.5
2. B. E.	M	19	Rheumatic fever with pancarditis	Cortisone	8.9	5.7
3. H. A.	M	33	Chronic rheum. arthritis	Cortisone	12.2	5.0
4. M. E.	M	40	Chronic rheum. arthritis	Cortisone	11.3	6.7
5. F. A.	M	69	Chronic rheum. arthritis	Cortisone	8.4	5.8
6. K. L.	F	59	Bronchial asthma	Cortisone	5.2	2.3
				later ACTH		6.4
7. O. F.	M	49	Acute rheum. arthritis	ACTH	6.3	12.3
8. B. M.	F	54	Acute rheum. arthritis	ACTH	4.6	12.6
9. H. B.	F	69	Chronic rheum. arthritis	ACTH	2.3	9.0
10. W. A.	F	54	Chronic rheum. arthritis	ACTH	4.9	7.7
11. H. F.	M	39	Acute rheum. arthritis	ACTH	8.8	9.7
12. H. L.	F	48	Spastic colitis	ACTH	1.5	12.2
13. H. L.	F	54	Bronchial asthma	ACTH	6.4	16.3
14. D. C.	F	49	Chronic eczema	ACTH	2.9	12.1
15. M. G.	M	42	Gout arthritis	ACTH	3.1	17.5
16. M. E.	M	36	Lupus erythematosus	ACTH	3.6	7.5 2.5 2 wks. later
17. K. K.	M	33	Status post-castration	ACTH	4.8	9.0
18. B. A.	M	48	Panmyelopathia	ACTH	11.6	16.0
19. S. R.	F	55	Panhypopituitarismus	ACTH	0.9	3.7

III. DISCUSSION

The cases studied in this survey covered a wide spectrum of diseases in internal medicine. The results demonstrated that certain groups of diseases affect directly or indirectly the 17-K. S. output. These include adrenal cortical and pituitary hypofunction, thyroid hypo and hyperfunction, and male hypogonadal function, as endocrine dysfunctions, parenchymal liver disease, chronic metabolic disorders, and chronic debilitating illnesses. The severity and the duration of the illness were recognized to be contributory factors in reducing the output.

Because the adrenal cortex is responsible for the secretion of the major part of the precursor substances of the 17-K. S., hypofunction of this organ results regularly in a low 17-K. S. excretion. This has been established by many authors (10, 11, 12, 13), and was also confirmed in this study. The actual cause of the adrenal cortical insufficiency is attributed indirectly either to a reduced function of the anterior pituitary or directly to adrenal cortical pathology, as in Addison's disease.

The effects are more pronounced in females where the adrenal cortex represents the only organ producing significant amounts of androgens. Their total 17-K. S. output may reach low or even 0 values. The values may also be significantly reduced in males. However, the fact that precursor substances are produced to some extent in the testes prevents the male output from reaching the low values that are found in females, unless some associated testicular hypofunction is present.

On the other hand hyperfunction of the adrenal cortex usually causes significant increases in 17-K. S. excretion. The cause is in most cases a tumor or hyperplasia of the cortical tissue (16). Abnormally high outputs may also be found in young males suffering from precocious puberty due to Leydig cell tumors (15).

The highest values of 17-K. S. output have been reported in cases of carcinoma of the adrenal cortex, with somewhat lower values in adenomas and adrenal cortical hyperplasia (16). These may appear clinically in the form of the adrenogenital syndrome. However, some cases have been reported in which adrenal cortical tumors were present without any significant increase in 17-K. S. excretion (14).

The results of 17-K. S. output in cases of Cushing's disease have been reported in the literature to be a high normal or slightly elevated above the norm (10). One of the 3 cases in this survey had a similar excretion, namely, 16.2 mg. (F) in 24 hours.

As anticipated, patients suffering with pituitary hypofunction were found to excrete extremely small quantities of 17-K. S. The values were 6.4 (M), 1.5 (F), 0.8 (F), and 0.9 (F) mg. in 24 hrs.

In addition to abnormal urinary output of the 17-K. S. in adrenal and pituitary disorders, it was found that other endocrine disorders may also produce abnormal results. Orchidectomy and castration in males

is followed by some reduction in 17-K.S. output. In this survey the values of these patients were 2.9, 4.8, 8.1, and 3.2 mg. in 24 hrs. The androgens secreted by the testes theoretically contribute one third to the total amount of 17-K.S. excreted, and hypogonadism has been reported to produce total excretions within the lower limit (3). Actually, the reducing effect may be even greater as observed in 3 of the 4 cases studied in this survey. There is, however, no concrete explanation except that there may be some indirect effect on the adrenal cortex.

The average excretion of 17-K. S. in patients with hyperthyroidism and myxedema has been reported to be below normal in both sexes (17). This was amply confirmed by the results of the thyroid patients in this survey. In the cases of thyroid insufficiency, low outputs were measured, namely, 4.5 and 3.1 mg. both in females. In the only case of hyperthyroidism the patient, a male, excreted only 3.4 mg. in 24 hrs. The mechanism causing the reduced output in these conditions is, however, not clear, although the metabolism of the thyroid seems to be in some way to be related to the function of the adrenal cortex.

The administration of estrogens in virilism has been found to diminish the high output of 17-K. S. (13). Furthermore, Hamblen et al (8) showed that a correlation exists between the duration of amenorrhea (in ovarian failure) and the amount of 17-K. S. excretion. Their findings indicate that late or intercurrent estrogenic failure precipitates androgenic hyperfunction of the adrenal cortex. They found that definite elevations in titer occurred in patients with intercurrent amenorrhea which had lasted 6 months or more. They also found that simple corpus luteum failure of the ovaries was not followed by secondary hyperactivity of the adrenal cortex, and therefore any change in the function of the corpus luteum had no effect on the level of the 17-K. S. (19).

The results of the survey revealed that patients with metabolic and deficiency disorders may excrete reduced quantities of 17-K.S. These disorders included diabetes mellitus, sprue, dysproteinemia, and gout. Forbes et al (4) also reported lower than normal excretion values in patients suffering from diabetes, sprue, and malnutrition from anorexia. Sposita and Pelosia (20) found in their survey of 15 cases of diabetes mellitus that these patients excreted below normal quantities of 17-K. S. They reported, however, that these low values returned to normal subsequent to the administration of insulin.

In this survey of diabetic patients it was demonstrated that the younger patients and those individuals who had been ill for a relatively short time had normal 17-K.S. outputs (Table 5, cases No. 1, 2, 8, 9), while the older and more severely ill patients had significantly lower excretions (Cases No. 3, 4, 5, 7). Severity and duration therefore appear to be active factors associated with reduced output. There is actually no clear out evidence to suggest that the disease itself causes the change in output. What is suggestive, however, is that the disease may act as any

debilitating disease in causing a generalized reduction in function of the vital processes of the body, including the adrenal cortex.

In the cases of sprue and dysproteinemia, severe malnutrition was present, causing what has been described as a degradation effect of steroid excretion in chronic debilitating disease.

17-K. S. excretion in gout has been described by Wolfson and his workers (21). They found a significant reduction in output in all of their patients during all stages of the disease, including the asymptomatic interval. In the one case observed in this survey the output was also very low, 3.1 mg. (M) in 24 hrs. There is, however, no available explanation for this reduced output except that some altered adreno-cortical function is present.

Patients suffering from chronic debilitating and malnutrition diseases have been reported to have reduced 17-K. S. excretion (11, 12, 4). Pearlman (22), found that cancerous persons excrete significantly less 17-K. S. than do normal individuals. In a series of 83 cases of pulmonary tuberculosis, Rivoire et al (23) reported the output varied directly with the severity and duration of the disease. Their values varied from normal in mild cases to almost 0 values in cases of cachexia. In an extensive survey by Forbes et al (4), it was reported that the average excretion for chronically ill patients was 6.2 mg. in males, and 4.4 mg. in females, as compared to 12.5 and 8.2 mg. respectively. In other reports, it was revealed that normal 17-K. S. excretion was present in patients suffering from tetra and paraplegia (24), while a reduction was observed in patients suffering from trauma and infection (25). On the other hand, it was found that a temporary increase in output is present during stress, as for example during examinations or during flying (26).

Although several exceptions were noted, it was found that the results of this survey corresponded to these earlier reports. The more chronic and the more severe the illness, the greater was the reduction in output. The cause of the reduced output is not clear although it is believed to be due to a decrease in adrenal cortical secretion in chronic disease. The quantity found in the urine is the result of various metabolic transformations that occur within the body, and it may be that in various chronic diseases degradation rates of the steroids are different.

It has been known for some time that the 17-K. S. output is significantly reduced in parenchymatous liver disease. This is true for both acute and chronic diseases of this organ.

In a large series of cases of acute infections hepatitis, Bjørneboe et al (28) observed low 17-K. S. excretion in each of these patients. The results were considerably lower in the first 2—3 weeks of the illness but gradually rose to normal values in the succeeding few weeks. He also observed that the more severe the case was, the longer did it take for the value to return to normal. These results were confirmed by other

workers (29, 30 and 31), and the 5 cases of infectious hepatitis in this survey behaved correspondingly.

Low 17-K. S. excretion in Laennec liver cirrhosis has been reported by several authors (30, 31, 32, 33, 34, 36 and 42) and was confirmed by the results in 15 cases in this survey.

Weller (31) observed 3 cases of obstructive jaundice. One case, a relatively early one, had a normal 17-K. S. excretion value. In the other 2 cases, which had been known to exist for some time, the output was reduced. The one case observed in this survey likewise existed for some time, and the value was 4.0 (F) mg. in 24 hrs.

Justin-Besançon (37) reported one case of hemachromatosis with cirrhosis where the 17-K. S. output was markedly reduced and the one case in this survey was also of a low value, 3.6 (M) mg. in 24 hrs.

Explanation for the reduced output of the 17-K. S. is based on the following theoretical and experimental work:

It is known that the estrogen content of the body increases significantly in the presence of parenchymatous liver disease. This has been explained very logically by Zondek and Selye who showed that the estrogens are inactivated in the liver; and when this organ is diseased this function is reduced. As a result of an increase in the presence of these hormones, feminization signs, as found in liver cirrhosis, are produced. Morrione (41) found that the increase in estrogens in these cases was responsible for the development of testicular atrophy. Lloyd and Williams (3) further believe that the increase in the estrogen content produces a depressive action on the anterior pituitary, causing a decrease in the amount of gonadotrophic hormones and ACTH secreted. Thus the function of the adrenal cortex and the gonads is reduced with a subsequent reduction in 17-K. S. excretion.

Pincus (38) has described the liver as the central area for the breakdown of the androgens followed by their detoxification there through esterification with sulfuric and glucuronic acids. It is in this form that they are excreted in the urine. However, this mechanism is injured in liver disease and a reduced 17-K. S. output follows (39).

A further factor to be considered is the injury effect these diseases have on the adrenal cortex itself. Forbes et al (4) have shown conclusively that the 17-K. S. level normally responds to all kinds of bodily injury, trauma or disease, by a transient increase for one to a few days duration, followed by a marked depression with a final return to a normal value during convalescence. Some evidence for this lies in the fact that significant increases in the 17-K. S. output occurs following injections of free testosterone or testosterone propionate, which would imply that the liver is still functioning while the adrenal cortex is depressed.

In cases of liver damage, however, the injury effect to the adrenal cortex plays a much smaller role. Samuels et al (40) demonstrated high blood levels of testosterone in the blood and urine of rabbits and rats

when the livers of these animals were removed. Marti (30, 42) found that by i. m. or i. v. injection of testosterone propionate into patients with liver cirrhosis or epidemic hepatitis and normal persons that the cirrhotic and hepatitis patients excreted comparatively slight increases in 17-K. S., while the normal controls excreted correspondingly greater quantities (see Fig. 2). In liver cirrhosis there is a significant damage to and loss of function of the parenchyme. Consequently, a hormonal disturbance exists (feminism) while the inability of the liver to detoxify the androgenic substances explains the low 17-K. S. output in this disease. The traumatic or acute effect on the adrenal cortex applies in liver diseases only to cases of infectious hepatitis, where the body is only temporarily shaken so that the effect on the adrenal cortex is only transitional.

The results of this survey corresponded with those of other workers and with the theoretical expectations. In only one case of liver cirrhosis was the 17-K. S. output in the normal range (Table 4, case No. 4, 14.9 mg.) Since no determination was made before the illness, we can only surmise that the output was in the upper limits or above normal then.

The results of the laboratory tests for liver function were in most cases typical of those expected in liver cell disease. There were, however, some exceptions, where despite the fact positive clinical signs were present, some of the laboratory tests were negative. Yet in each case the 17-K. S. output was reduced. The question then arises, is the determination of the 17-K. S. output a more sensitive means of measuring the presence and the extent of liver damage than the classical laboratory function tests. This may very well be possible although to prove it, it would be necessary to know the 17-K. S. output and liver function tests before the onset of the disease, and compared again during the progress of the disease. However, this test may still be valuable in following the progress of these diseases. A good example can be cited with the following case:

Case Report

The patient was a 48 yr. old woman who was admitted to the hospital with bleeding esophageal varices, a complication of a long-standing Laennec liver cirrhosis. She had a long history of chronic alcoholism. Symptoms, namely, anorexia, nausea, and vomiting began several months prior to her admission.

Examination revealed a pale, poorly nourished woman who appeared seriously ill. She complained of pain in the left upper quadrant which radiated to the right side. She was vomiting constantly and the vomitus contained what appeared to be bile. Although her sclerae were yellow-tinged there were no other signs of jaundice. Telengiectases were present on her nose and cheeks. Her heart and lungs were negative. Her liver was vastly enlarged, extending down to the iliac crest. The spleen was palpable. The axillary and pubic hair was scanty. The stools were melenous and the urine was colored yellow. Laboratory results were as follows: Cephalin flocc., Weltmann reaction — 0.20, Quick — 80%, Bromsulphalein retention — I 17% — 15 min. II 6% — 30 min., Serum bilirubin 2.9 mg.%, Alk. phosphatase — 16.6 Bodansky units, and 17 — K. S. output — 5.5 mg. Sedimentation rate — 58/61 mm, Hb — 62% and a macrocytic anemia. During her stay in the hospital the patient responded well to treatment and was discharged 6 weeks following admission.

Four months later, she was again admitted to this hospital because of esophageal bleeding. At this time she was very weak and practically in a state of shock. Clinical signs were identical with those of the time of her previous admission except the liver was somewhat smaller, harder and more nodular. Jaundice was also present. Liver tests revealed some reduction in function: Cephalin flocc., Weltmann reaction — 0.18, Quick — 70%, Bromsulphthalein retention — I 18% II 6%, Serum bil. — 4.8 mg.%, and her 17-K.S. output was markedly reduced to 1.1 mg. During this stay she was transferred to surgery where an operation was performed to relieve the collateral circulation. The hepatic and splenic arteries were ligated and a side to side anastomosis was made between the inferior vena cava and the portal vein. The patient improved and was discharged from the clinic 5 weeks subsequent to this admission.

Four months later, she was again admitted to the hospital suffering from severe bleeding and expired during the night from a loss of blood and shock despite several transfusions.

In this case the classical liver function tests appeared positive before the 17-K. S. output was reduced to below normal. However, there was no knowledge of the 17-K. S. output in the premorbid or in the early stage of her illness. The fact that her output was only 5.5 mg. on her first admission may mean that some reduction had already taken place since this value is in the lower limit of normal. It was also observed that output reduced markedly with the progress of the disease, 5.5 to 1.1 mg./24 hrs., the latter determination having been made about 4 months before she expired.

IV. CONCLUSION

From the results of this survey and from the evidence presented by several authors, certain conclusions can be drawn concerning the influence of internal diseases on 17-K.S. output. The quantity of 17-K.S. in the urine generally reflects the degree of adrenal cortical and testicular function and contributes evidence of any abnormal activity in these organs. Although extremes may represent inaccurate collections or minor illnesses, the wide variation indicates that a single determination must be very high or very low to have diagnostic value.

The test has proven to be of most value in adrenal cortical failure, primary or secondary. It is also used to bolster the clinical evidence in adrenal cortical hyperfunction in patients with virilism due to either tumor formation or glandular hyperplasia.

The abnormally low values of the steroids is in itself of no specific diagnostic significance, since a reduced 17-K.S. output appears in many non-specific chronic and debilitating diseases. This suggests that adrenal cortical hormone metabolism may undergo qualitative changes not only under conditions of direct adrenal pathology but also in response to physiologic stress. Therefore the 17-K. S. value may serve as a good indication of the general state of the body and its function.

The 17-K.S. determination has no diagnostic value in Cushing's disease because the results are too non-specific.

The results and reports described offer conclusive evidence that the liver plays a significant role in the metabolism of the androgens in so far as the transformation of testosterone to 17-ketosteroids, and therefore any change in function of this organ is reflected in a marked delay and reduction in output of the 17-K.S. In this way the determination of the 17-K.S. may serve as a further test of liver function. One of the main difficulties in the interpretation of this test is the fact that usually we do not know the premorbid excretion value of the patient. A person with an output in the normal upper range when in the healthy state may still have a normal output, although in the lower limit, when suffering from a liver disease. However, during the course of the illness, determinations may serve as an aid in measuring the progress of the disease.

V. SUMMARY

1. A survey was made of 138 cases from the medical department of the University cantonal hospital in Zürich to determine the effects of internal diseases on 17-ketosteroid excretion.

2. The results indicated that low values are present in patients suffering from adrenal cortical insufficiency, hypopituitarism, hypo and hyperthyroidism, male hypogonadism, and furthermore, from any chronic debilitating and malnutrition disease. Especially low results were observed in patients in this study suffering from parenchymal liver disease.

Low results were also observed in cases of acute infection and trauma when the adrenal cortex is temporarily exhausted.

3. The administration of testosterone was found to produce only a slight rise in 17-K.S. output in patients with liver disease as compared to much higher increases in healthy individuals.

4. The low excretion of 17-K.S. explains in part the clinical finding of feminine hair distribution in cases of liver cirrhosis.

5. The finding that ACTH causes an increase in 17-K.S. excretion while cortisone is responsible for a reduced output, was confirmed.

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Grateful acknowledgement is made to Prof. Dr. Wilhelm Löffler for the opportunity to perform this study, and to Dr. Fritz Koller who supervised this study, for his careful guidance, his helpful suggestions, and instruction, and his encouragement throughout the period of work.

The determinations of the 17-ketosteroids were performed in the hormone laboratory of the medical Poliklinik. I should like to express my gratitude to Prof. P. H. Rossier as well as to the members of the laboratory for making available the many results reported in this study.

Acknowledgement is also due to Dr. Max Marti of the Koller research laboratory for his explanation of certain theoretical and technical aspects of the subject of study and his permission to use the results of his experimental work.

I should also like to express my appreciation to the archiv staff of the medical department for making available the case histories and research material.

CURRICULUM VITAE

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